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EXAMINER	
JARRELL, NOBLE E	
ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/595,939	MERCEP ET AL.	
	Examiner	Art Unit	
	NOBLE JARRELL	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-11 and 22* is/are rejected.

7)☒ Claim(s) *8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/2/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

1. The objection raised in the 1 October 2008 rejection has been overcome by the amendment filed 2 February 2009 because claim 21 has been cancelled.

2. In the currently amended set of claims, claims 1-11 and 22 are pending. Claims 12-21 have been cancelled.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 10 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions comprising compounds of formula I and salts thereof, does not reasonably provide enablement for solvates of formula I. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Consideration of the relevant factors sufficient to establish a *prima facie* case for lack of enablement is set forth herein below:

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to compounds composed with a 1-aza-2-oxa-dibenzo[*e*, *h*]azulene core structure where variable X is an O, C, $S(O)_{0-2}$, or N. Compositions comprising these compounds as well as a method of preparing these compounds are claimed as well.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

Vippagunta et al. (*Advanced Drug Delivery Reviews*, **2001**, *48*, 3-26, cited in previous office action) teach that solvate formation is unpredictable due to the unique chemical nature of compounds, even among a series of related compounds (page 18, section 3.4).

(5) The relative skill of those in the art:

Those of relative skill in the art are those with level of skill of the authors of the references cited to support the examiner's position. The relative skill of those in this art is MD's, PhD's, or those with advanced degrees and the requisite experience in preparation of compounds of formula I as well as solvate preparation.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for the preparation of compounds of formula I and salts thereof.

However, the specification does not provide guidance for solvate of formula I.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to claim 10 and the high unpredictability in the art as evidenced therein, and the lack of guidance

provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims. **This rejection is maintained because applicants have not shown that they are able to make solvates of compounds formula I.**

5. Claims 1-7 and 9-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds of formula I where variable Y is H and Z is hydrogen (when variable X is oxygen or sulfur), halogen (when variable X is oxygen or sulfur), alkoxy (when X is sulfur), thioalkyl (when variable X is oxygen), alkyl (when variable X is oxygen), and nitro (when variable X is oxygen), does not reasonably provide enablement for any other instances of variables Y and Z in formula I. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Consideration of the relevant factors sufficient to establish a *prima facie* case for lack of enablement is set forth herein below:

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to compounds composed with a 1-aza-2-oxa-dibenzo[*e*, *h*]azulene core structure where variable X is an O, C, $S(O)_{0-2}$, or N. Compositions comprising

these compounds as well as a method of preparing these compounds are claimed as well.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

A substructure in the Sigma-Aldrich catalog ("Substructure search", http://www.sigmaaldrich.com/catalog/search/substructuresearchpage, accessed 9/18/2008, cited in previous office action) teaches that two starting materials are commercially available for the reactant described on page 15 of the specification. The only two commercially available compounds are compounds where one, X is NMe, Y and Z are each hydrogen, and two, variable X is S, variable Y is H, and variable Y is chloro. Thus, only compounds with these groups can be prepared based upon commercial availability.

Ueda et al. (*Chemical and Pharmaceutical Bulletin*, **1975**, *23(10)*, 2223-2231, cited in IDS) teach that when variable X is sulfur, variable Y can be hydrogen and variable Z can be hydrogen, halogen, or alkoxy. When variable X is oxygen, variable Y can be H and Z can be hydrogen, halogen, alkoxy, thioalkyl, alkyl, and nitro (table IV, page 2228).

(5) The relative skill of those in the art:

Those of relative skill in the art are those with level of skill of the authors of the references cited to support the examiner's position. The relative skill of those in this art is MD's, PhD's, or those with advanced degrees and the requisite experience in preparation of compounds embraced by formula I.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for compounds of formula I where one, X is O and variables Y and Z are H, and two, X is S, Y is H or halogen, and Z is H. In addition, applicants are enabled for an instance of formula I where X is NMe and Y and Z are each H. Ueda et al. provide guidance for other groups (see above).

However, the specification does not provide guidance for the preparation of all compounds encompassed by formula I.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to claims 1-7 and 9-11 and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

6. Newly amended claims 11 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the *in vivo* testing of the prepared compounds in mice, does not reasonably provide enablement for treatment of any disease related to modulation of 5-HT_{2A}, 5-HT_{2C}, or σ1 receptors (in the amendment to the specification, page 21, treatment does not include prevention anymore). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Applicants are enabled for the *in vivo* testing of the prepared compounds in mice.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or

unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Consideration of the relevant factors sufficient to establish a *prima facie* case for lack of enablement is set forth herein below:

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to a method of inhibiting 5-HT_{2A}, 5-HT_{2C}, or σ1 receptors using compounds composed of a 1-aza-2-oxa-dibenzo[e, *h*]azulene core structure where variable X is either O, C, $S(O)_{0-2}$, or N. Thus, the claims taken together with the specification imply that trauma or brain stroke can be treated through modulation of these receptors.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

Legos et al. (*Expert Opinions on Investigational Drugs*, **2002**, *11(5)*, 603-14) teach that several developmental issues exist before a realistic therapy for strokes can be developed (section 7, page 609). These issues include: reduction in excitotoxicity or disruptions in ionic homeostasis; narrow therapeutic range; patient selection (due to a heterogeneous population); and other variables that are part of clinical trials. Legos et al. also state the treatment of neurodegenerative diseases is a potential target for therapeutic agents (section 6, page 609). Partial restoration of blood flow to the misery perfused areas of the brain may help to facilitate the development of traditional neuroprotective therapies. This teaching shows that future research is needed to determine if neurodegenerative diseases are a viable target for therapy.

(5) The relative skill of those in the art:

Those of relative skill in the art are those with level of skill of the authors of the references cited to support the examiner's position. The relative skill of those in this

art is MD's, PhD's, or those with advanced degrees and the requisite experience in neurodegenerative diseases linked to modulation of 5-HT_{2A}, 5-HT_{2C}, or σ1 receptors.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for *in vivo* testing of the prepared compounds in mice.

However, the specification does not provide guidance for treatment of a neurodegenerative disorder.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to claims 11 and 22 and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Newly amended claims 11 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. What specific neurodegenerative diseases are being treated by administration of compounds of formula I? The National Library of Medicine lists neurodegenerative diseases that are affect different part of the nervous system ("Neurodegenerative Diseases", http://www.nlm.nih.gov/cgi/mesh/2008/MB_cgi, Accessed 8 December 2008, attached as PDF). Thus, it is unclear what type of neurodegenerative disorder is being treated.

Conclusion

9. Claim 8 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

10. The following is a statement of reasons for the indication of allowable subject matter: Compounds of formula I appear free of the prior art of record. Fieser et al. (*Journal of the American Chemical Society*, **1933**, *55*, 4963-76, cited in previous action) teach compound III (page 4964). This compound fails to anticipate or render obvious compounds of formula I because variable X is C(O) and the ring is pentacyclic, not tetracyclic.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NOBLE JARRELL whose telephone number is (571)272-9077. The examiner can normally be reached on M-F 7:30 A.M - 6:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Noble Jarrell/
Examiner, Art Unit 1624

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624